

## EXHIBIT A

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## Structure-activity relationships of the inhibitory effects of flavonoids on P-glycoprotein-mediated transport in KB-C2 cells.

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We studied the effects of flavonoids, naringenin (flavanone), baicalein (flavone), kaempferol, quercetin, myricetin, morin, and fisetin (flavonols) as well as two glycosides of quercetin on P-glycoprotein (P-gp) function in multidrug-resistant P-gp overexpressing KB-C2 cells. Flavonoids such as kaempferol and quercetin increased the accumulation of rhodamine-123 dependent on their chemical structure. Analysis by flow cytometry indicated that the increase in substrate accumulation was due to the inhibition of substrate efflux. Naringenin, which lacks the 2,3-double bond in the C ring, had no effect, although it was more hydrophobic than myricetin, fisetin and morin. Therefore, the planar structure of the flavonoids seemed to be important for their interaction with P-gp. The effects of other flavonoids on the accumulation of daunorubicin were in the order of kaempferol>quercetin, baicalein>myricetin>fisetin, morin. Quercetin-3-O-glucoside and rutin had no effect. The order of the effects corresponded with that of the partition coefficients. Difference in the number and position of hydroxyl groups in flavonoid molecules by themselves seemed to have little effect. These results suggested that hydrophobicity as well as planar structure is important for the inhibitory effects of flavonoids on P-gp-mediated transport.

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